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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,469	08/20/2003	Richard A. Shimkets	Cura-904	6214

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/644,469	SHIMKETS ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 15-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-14 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0105*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 03/10/2006 has been entered. Claims 1–29 are pending.

Applicant's election of group III, claims 9–14, in the reply filed on 03/10/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1–8 and 15–25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/10/2006.

Claims 9–14 and 26–29 are being examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9–14 and 26–29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 9–13 and 26 are directed to or encompass a method of diagnosing any hypophosphatemic condition comprising measuring the level of FGF-7 protein in any biological sample or in blood or urine. Claims 14 and 27–28 are directed to or encompass a method of diagnosing osteomalacia (any condition marked by softening of the bones, See MeSH search for

"Osteomalacia") comprising measuring the level of FGF-7 protein in any biological sample or in blood or urine. The following passages from the specification seem most relevant for construing the nature of the claimed invention:

> Hypophosphatemia has many causes including decreased dietary intake of phosphorus-containing foods, decrease in intestinal absorption, increased excretion into the urine, renal failure, and medications. Unfortunately, the finding of hypophosphatemia is not a reliable indicator of deficiency, since total-body deficiency of phosphorus may be found in a patient's with hyperphosphatemia with, for example, diabetic ketoacidosis. Page 1, lines 23–27.

> One such acquired disorder of phosphate homeostasis is oncogenic osteomalacia which is also referred to as tumor-induced osteomalacia (TIO). TIO is marked by renal phosphate-wasting disorder resulting in low serum phosphorus concentration and osteomalacia. Removal of the tumor normalizes phosphate metabolism. Additionally recent studies have identified that phosphatonin to be identical to fibroblast growth factor 23 (FGF-23) (Shimada et al, Proc. Natl. Acad. Sci., 2001, vol:98, 6500-6505). FGF-23 is the recently identified member of the FGF family. While previous studies suggest that overproduction of FGF23 causes TIO, there is speculation that mutation in FGF-23 gene results in autosomal dominant hypophosphatemic rickets (ADHR) (White et al, Nat. Genet. 2000, 26:345-348). ADHR is yet another phosphate wasting disorder resulting in low serum phosphorus concentration, rickets and osteomalacia. Previous studies show no evidence that recombinant FGF-23 can inhibit phosphate uptake in renal proximal epithelial cells. Page 6, full paragraph 1.

> Proper serum phosphate concentrations are maintained by a complex and poorly understood process. Identification of genes responsible for inherited disorders involving disturbances in phosphate homeostasis may provide insight into the pathways that regulate phosphate balance. Page 7, full paragraph 2.

> Figure 3 shows that FGF 7 can inhibit Phosphate transport in a dose-dependant manner within the physiological range. Furthermore, Figure 4 demonstrates that FGF-7 antibody can reverse FGF-dependent Phosphate transport inhibition in renal epithelial cells. Page 12, lines 23–26.

The specification provides results demonstrating quantitatively higher FGF7 protein levels in the conditioned media from the cultures of tumors explanted from two patients identified as having tumor induced osteomalacia (TIO) (Example 3, page 12).

As indicated above, hypophosphatemia has many causes and proper serum phosphate concentrations are maintained by a complex and poorly understood process. Tumor-induced osteomalacia (TIO) is only one such acquired disorder of phosphate homeostasis. No further examples of higher FGF7 protein levels in any other condition are provided. The examiner is aware that working examples are not required. Lack of working examples, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. A skilled artisan does not have any guidance as to other hypophosphatemic conditions in which FGF7 protein levels are elevated or diagnostic. The study of rare disorders associated with renal phosphate wasting has resulted in the discovery of a number of proteins [fibroblast growth factor 23 (FGF-23), secreted frizzled related protein 4 (sFRP-4), matrix extracellular phosphoglycoprotein, and FGF 7 (FGF-7)] that decrease renal sodium-dependent phosphate transport in vivo and in vitro. See Berndt (Am J Physiol Renal Physiol. 2005 Dec;289(6):F1170-82), page F1170, Abstract. The specification discloses that approximately 4000 gene fragments were analyzed using GeneCalling on the osteomalacia patient samples. Of these, only 12 fragments were consistently upregulated in cells positive for the phosphate transport inhibiting activity which are shown in Figure 2. Six of the twelve are secreted proteins that are known in the public domain: Glia-derived neurite promoting factor (GDNPF), Homo sapiens insulin-like growth factor binding protein 5, Homo sapiens Osteoprotegrin ligand, Homo sapiens Cathepsin B, Homo sapiens FGF-7 (KGF), and Homo sapiens CD4. See the specification at page 12. Applicants' results did not identify FGF-23, sFRP-4, or matrix extracellular phosphoglycoprotein. A study of genes differentially expressed in oncogenic osteomalacia did not identify FGF7 overexpression. See De Beur (J Bone Miner Res. 2002 Jun;17(6):1102-10),

Tables 2 and 3. Current models of phosphate homeostasis indicate that renal phosphate wasting could result from: 1) mutations in a gene that enables the organism to assess extracellular phosphate concentrations (a phosphate sensor or phosphate sensing system); 2) activating mutations in a gene(s) that codes for a renal phosphate wasting hormone ("phosphatonin") or its receptor (including associated G proteins or other effector molecules); 3) mutations in a gene(s) that codes for a phosphate-conserving hormone or its receptor; 4) mutations in genes that code for repressors or inducers for the above hormones; 5) mutations in genes that code for enzymes that activate or degrade these hormones (as is likely to be the case with the PHEX gene); and 6) mutations in genes that code for the sodium-dependent phosphate cotransporters. See Econs (Bone. 1999 Jul;25(1):131-5), page 133, right column, full paragraph 1. It seems apparent that renal phosphate wasting is associated with numerous factors, each of whose relevance would vary from individual to individual. Therefore, it is reasonable to conclude that an invention directed to the diagnosis of any hypophosphatemic condition or any condition marked by softening of the bones by measuring FGF7 levels is highly unpredictable and variable. Moreover, it is not known whether FGF7 circulates in plasma or whether it is elevated in the plasma of subjects with any hypophosphatemic condition or any condition marked by softening of the bones. See Berndt (Am J Physiol Renal Physiol. 2005 Dec;289(6):F1170-82), page F1178, paragraph bridging left and right columns. In this same paragraph Berndt also indicates the complexity of factors involved in the pathogenesis of tumor-induced osteomalacia. The specification does not provide any guidance regarding the presence of FGF7 in urine. The specification also lacks guidance as to the appropriate biological samples in which to detect elevated levels of FGF7 protein. Applicants should provide substantial evidence of a diagnostic

utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan would accept without question that elevated FGF7 protein levels are diagnostic of any hypophosphatemic condition or any condition marked by softening of the bones or that elevated levels of FGF7 protein could be detected in the blood or urine of any patient afflicted with such conditions. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the complexity of factors involved in renal phosphate homeostasis in general and the pathogenesis of tumor-induced osteomalacia in particular, and the unpredictability in the art, it would require undue experimentation for the skilled artisan to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9–13 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9–13 and 26 are indefinite over the recitation of "hypophosphatemic condition" because it is unclear if hypophosphatemia is diagnosed or a condition associated with hypophosphatemia is diagnosed. The metes and bounds are not clearly set forth.

Claim Objections

Claim 14 is objected to because of the following informalities: "osteomalacia" (line 5) is misspelled. Appropriate correction is required.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
APRIL 30, 2006